

SEQUENCE LISTING

<110> Tang, Jordan J.N.

Hong, Lin

Ghosh, Arun K.

<120> Inhibitors of Memapsin 2 and Use Thereof

<130> OMRF 182

<140> Not Yet Assigned

<141> 2000-06-27

<150> 60/141,363

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<150> 60/210,292

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<160> 31

<170> PatentIn Ver. 2.1

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<212> DNA

<213> Homo sapiens

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<211> 488
 <212> PRT
 <213> Homo sapiens

 <220>
 <223> Purified Memapsin 2

 <220>
 <223> Amino Acids 28-48 are remnant putative propeptide residues

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 <223> Amino Acids 58-61, 78, 80, 82-83, 116, 118-121, 156, 166, 174, 246, 274, 276, 278-281, 283, and 376-377 are residues in contact with the OM99-2 inhibitor

 <220>
 <223> Amino acids 54-57, 61-68, 73-80, 86-89, 109-111, 113-118, 123-134, 143-154, 165-168, 198-202, and 220-224 are N-lobe Beta Strands

 <220>
 <223> Amino Acids 184-191 and 210-217 are N-lobe Helices

 <220>
 <223> Amino acids 237-240, 247-249, 251-256, 259-260, 273-275, 282-285, 316-318, 331-336, 342-348, 354-357, 366-370, 372-375, 380-383, 390-395, 400-405, and 418-420 are C-lobe Beta Strands

 <220>
 <223> Amino Acids 286-299, 307-310, 350-353, 384-387, and 427-431 are C-lobe Helices

 <400> 2
 Ala Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro
 1 5 10 15

 Leu Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg
 20 25 30

 Glu Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val
 35 40 45

 Glu Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val
 50 55 60

Glu Met Thr Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp			
65	70	75	80
Thr Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu			
	85	90	95
His Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg			
	100	105	110
Lys Gly Val Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu			
	115	120	125
Gly Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg			
	130	135	140
Ala Asn Ile Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly			
145	150	155	160
Ser Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg			
	165	170	175
Pro Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr			
	180	185	190
His Val Pro Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro			
	195	200	205
Leu Asn Gln Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile			
	210	215	220
Gly Gly Ile Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro			
225	230	235	240
Ile Arg Arg Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile			
	245	250	255
Asn Gly Gln Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys			
	260	265	270
Ser Ile Val Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val			
	275	280	285
Phe Glu Ala Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys			
	290	295	300
Phe Pro Asp Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala			
305	310	315	320

Gly Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met
325 330 335

Gly Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln
340 345 350

Tyr Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr
355 360 365

Lys Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val
370 375 380

Ile Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile
385 390 395 400

Gly Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala
405 410 415

Ala Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr
420 425 430

Asn Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val
435 440 445

Met Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val
450 455 460

Cys Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe
465 470 475 480

Ala Asp Asp Ile Ser Leu Leu Lys
485

<210> 3

<211> 503

<212> PRT

<213> Homo sapiens

<220>

<223> Pro-memapsin 2

<220>

<223> Amino Acids 1-15 are vector-derived residues

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<223> Amino Acids 16-64 are a putative pro peptide

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<223> Amino Acids 1-13 are the T7 promoter

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<223> Amino Acids 16-456 are Pro-memapsin 2-T1

<220>

<223> Amino Acids 16-421 are Promemapsin 2-T2

<400> 3

Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg Gly Ser Met Ala
1 5 10 15

Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu
20 25 30

Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu
35 40 45

Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu
50 55 60

Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu
65 70 75 80

Met Thr Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr
85 90 95

Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His
100 105 110

Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys
115 120 125

Gly Val Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly
130 135 140

Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala
145 150 155 160

Asn Ile Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser
165 170 175

Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro
180 185 190

Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His
195 200 205

Val	Pro	Asn	Leu	Phe	Ser	Leu	Gln	Leu	Cys	Gly	Ala	Gly	Phe	Pro	Leu	210	215	220	
Asn	Gln	Ser	Glu	Val	Leu	Ala	Ser	Val	Gly	Gly	Ser	Met	Ile	Ile	Gly	225	230	235	240
Gly	Ile	Asp	His	Ser	Leu	Tyr	Thr	Gly	Ser	Leu	Trp	Tyr	Thr	Pro	Ile	245	250	255	
Arg	Arg	Glu	Trp	Tyr	Tyr	Glu	Val	Ile	Ile	Val	Arg	Val	Glu	Ile	Asn	260	265	270	
Gly	Gln	Asp	Leu	Lys	Met	Asp	Cys	Lys	Glu	Tyr	Asn	Tyr	Asp	Lys	Ser	275	280	285	
Ile	Val	Asp	Ser	Gly	Thr	Thr	Asn	Leu	Arg	Leu	Pro	Lys	Lys	Val	Phe	290	295	300	
Glu	Ala	Ala	Val	Lys	Ser	Ile	Lys	Ala	Ala	Ser	Ser	Thr	Glu	Lys	Phe	305	310	315	320
Pro	Asp	Gly	Phe	Trp	Leu	Gly	Glu	Gln	Leu	Val	Cys	Trp	Gln	Ala	Gly	325	330	335	
Thr	Thr	Pro	Trp	Asn	Ile	Phe	Pro	Val	Ile	Ser	Leu	Tyr	Leu	Met	Gly	340	345	350	
Glu	Val	Thr	Asn	Gln	Ser	Phe	Arg	Ile	Thr	Ile	Leu	Pro	Gln	Gln	Tyr	355	360	365	
Leu	Arg	Pro	Val	Glu	Asp	Val	Ala	Thr	Ser	Gln	Asp	Asp	Cys	Tyr	Lys	370	375	380	
Phe	Ala	Ile	Ser	Gln	Ser	Ser	Thr	Gly	Thr	Val	Met	Gly	Ala	Val	Ile	385	390	395	400
Met	Glu	Gly	Phe	Tyr	Val	Val	Phe	Asp	Arg	Ala	Arg	Lys	Arg	Ile	Gly	405	410	415	
Phe	Ala	Val	Ser	Ala	Cys	His	Val	His	Asp	Glu	Phe	Arg	Thr	Ala	Ala	420	425	430	
Val	Glu	Gly	Pro	Phe	Val	Thr	Leu	Asp	Met	Glu	Asp	Cys	Gly	Tyr	Asn	435	440	445	
Ile	Pro	Gln	Thr	Asp	Glu	Ser	Thr	Leu	Met	Thr	Ile	Ala	Tyr	Val	Met	450	455	460	

Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys
465 470 475 480

Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala
485 490 495

Asp Asp Ile Ser Leu Leu Lys
500

<210> 4
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 4
Ser Glu Val Lys Met Asp Ala Glu Phe Arg
1 5 10

<210> 5
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 5
Ser Glu Val Asn Leu Asp Ala Glu Phe Arg
1 5 10

<210> 6
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 6

Ser Val Asn Met Ala Glu Gly Asp

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<210> 7

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 7

Lys Gly Gly Val Val Ile Ala Thr Val Ile Val Lys

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10

<210> 8

<211> 4

<212> PRT

<213> Homo sapiens

<400> 8

Asp Thr Ser Gly

1

<210> 9

<211> 8

<212> PRT

<213> Homo sapiens

<400> 9

Leu Val Asn Met Ala Glu Gly Asp

1

5

<210> 10

<211> 28

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Primer

<400> 10

ggtaagcatc ccccatggcc ccaacgtc

28

<210> 11
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 11
gacgttgggg ccatggggga tgcttacc

28

<210> 12
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

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acgttgtctt tgatcgggcc cgaaaacgaa ttgg

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<210> 13
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<212> DNA
<213> Artificial Sequence

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<223> Description of Artificial Sequence: Primer

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ccaattcggt ttcgggccc atcaaagaca acg

33

<210> 14
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 14
ccatccta atcgactcact atagggc

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<210> 15
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 15
actcactata gggctcgagc ggc 23

<210> 16
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 16
cttttgagca agttcagcct ggttaa 26

<210> 17
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<212> DNA
<213> Artificial Sequence

<220>
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<400> 17
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<210> 18
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 18
tggcgacgac tcctggagcc cg 22

<210> 19
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Primer

<400> 19
tgacaccaga ccaactggta atgg 24

<210> 20
<211> 27
<212> DNA
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<220>
<223> Description of Artificial Sequence: Primer

<400> 20
catatggcgg gaggctgcc tgccac 27

<210> 21
<211> 38
<212> DNA
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<220>
<223> Description of Artificial Sequence: Primer

<400> 21
ggatcctcac ttcagcagg agatgtcatc agcaaagt 38

<210> 22
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Oxidized
Insulin B-chain

<220>

<223> Xaa at site 3 represents cysteic acid

<400> 22

His Leu Xaa Gly Ser His Leu Val

1

5

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Oxidized
Insulin B-chain

<220>

<223> Xaa at site 1 represents cysteic acid

<400> 23

Xaa Gly Glu Arg Gly Phe Phe Tyr

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<210> 24

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 24

Val Gly Ser Gly Val

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<210> 25

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic
Peptide

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Val Gly Ser Gly Val Leu Leu
1 5

<210> 26

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 26

Gly Val Leu Leu Ser Arg Lys
1 5

<210> 27

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Inhibitors

<400> 27

Val Asn Leu Ala Ala Glu Phe
1 5

<210> 28

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Inhibitors

<400> 28

Glu Val Asn Leu Ala Ala Glu Phe
1 5

<210> 29

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 29

Asn Leu Ala Ala

1

<210> 30

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
Peptide

<400> 30

Val Gly Ser Gly Val Leu Leu Ser Arg Lys

1

5

10

<210> 31

<211> 326

<212> PRT

<213> Homo sapiens

<220>

<223> Amino acids 2-5, 6-9, 13-20, 25-32, 65-67, 69-74,
79-87, 89-91, 99-106, 119-122, 150-154, 164-167,
180-183, 191-194, 196-199, 201-204, 210-214,
221-223, 258-262, 265-269, and 275-278 are Beta
Strands

<220>

<223> Amino acids 281-284, 286-288, 298-301, 310-315,
and 319-324 are Beta strands

<220>

<223> Amino acids 48-51, 111-114, 136-142, 225-234,
249-254, 271-274, and 303-306 are Helices

<220>

<223> Amino acids 12-13, 30, 32, 34-35, 73-77, 111, 117,
120, 189, 213, 215, 217-220, 287, 289, 291, 298,
and 300 are residues in contact with pepstatin.

<220>

<223> Pepsin

<400> 31

Val Asp Glu Gln Pro Leu Glu Asn Tyr Leu Asp Met Glu Tyr Phe Gly
1 5 10 15

Thr Ile Gly Ile Gly Thr Pro Ala Gln Asp Phe Thr Val Val Phe Asp
20 25 30

Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Ser Ser Leu
35 40 45

Ala Cys Thr Asn His Asn Arg Phe Asn Pro Glu Asp Ser Ser Thr Tyr
50 55 60

Gln Ser Thr Ser Glu Thr Val Ser Ile Thr Tyr Gly Thr Gly Ser Met
65 70 75 80

Thr Gly Ile Leu Gly Tyr Asp Thr Val Gln Val Gly Gly Ile Ser Asp
85 90 95

Thr Asn Gln Ile Phe Gly Leu Ser Glu Thr Glu Pro Gly Ser Phe Leu
100 105 110

Tyr Tyr Ala Pro Phe Asp Gly Ile Leu Gly Leu Ala Tyr Pro Ser Ile
115 120 125

Ser Ser Ser Gly Ala Thr Pro Val Phe Asp Asn Ile Trp Asn Gln Gly
130 135 140

Leu Val Ser Gln Asp Leu Phe Ser Val Tyr Leu Ser Ala Asp Asp Gln
145 150 155 160

Ser Gly Ser Val Val Ile Phe Gly Gly Ile Asp Ser Ser Tyr Tyr Thr
165 170 175

Gly Ser Leu Asn Trp Val Pro Val Thr Val Glu Gly Tyr Trp Gln Ile
180 185 190

Thr Val Asp Ser Ile Thr Met Asn Gly Glu Ala Ile Ala Cys Ala Glu
195 200 205

Gly Cys Gln Ala Ile Val Asp Thr Gly Thr Ser Leu Leu Thr Gly Pro
210 215 220

Thr Ser Pro Ile Ala Asn Ile Gln Ser Asp Ile Gly Ala Ser Glu Asn

225		230		235		240
Ser Asp Gly Asp Met Val Val Ser Cys Ser Ala Ile Ser Ser Leu Pro						
	245		250		255	
Asp Ile Val Phe Thr Ile Asn Gly Val Gln Tyr Pro Val Pro Pro Ser						
	260		265		270	
Ala Tyr Ile Leu Gln Ser Glu Gly Ser Cys Ile Ser Gly Phe Gln Gly						
	275		280		285	
Met Asn Leu Pro Thr Glu Ser Gly Glu Leu Trp Ile Leu Gly Asp Val						
	290		295		300	
Phe Ile Arg Gln Tyr Phe Thr Val Phe Asp Arg Ala Asn Asn Gln Val						
305		310		315		320
Gly Leu Ala Pro Val Ala						
	325					